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Potential anticancer activity of protocatechuic acid loaded in montmorillonite/Fe_3O_4 nanocomposites stabilized by seaweed *Kappaphycus alvarezii*

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ABSTRACT

Superparamagnetic magnetite nanocomposites (Fe_3O_4-NCs) were successfully synthesized, which comprised of montmorillonite (MMT) as matrix support, *Kappaphycus alvarezii* (SW) as bio-stabilizer and Fe_3O_4 as filler in the composites to form MMT/SW/Fe_3O_4-NCs. Nanocomposite with 0.5 g Fe_3O_4 (MMT/SW/0.5Fe_3O_4) was selected for anticancer activity study because it revealed high crystallinity, particle size of 7.2 ± 1.7 nm with majority of spherical shape, and M_s = 5.85 emu/g with negligible coercivity. Drug loading and release studies were carried out using protocatechuic acid (PCA) as the model for anticancer drug, which showed 19% and 87% of PCA release in pH 7.4 and 4.8, respectively. Monolayer anticancer assay showed that PCA-loaded MMT/SW/Fe_3O_4 (MMT/SW/Fe_3O_4-PCA) had selectivity towards HCT116 (colorectal cancer cell line). Although MMT/SW/Fe_3O_4-PCA (0.64 mg/mL) showed higher IC_{50} than PCA (0.148 mg/mL) and MMT/SW/Fe_3O_4 (0.306 mg/mL, MMT/SW/Fe_3O_4-PCA showed more effective killing towards tumour spheroid model generated from HCT116. The IC_{50} for MMT/SW/Fe_3O_4-PCA, MMT/SW/Fe_3O_4 and PCA were 0.132, 0.23 and 0.55 mg/mL, respectively. This suggests the improved penetration efficiency and drug release of MMT/SW/Fe_3O_4-PCA towards HCT116 spheroids. Moreover, concentration that lower than 2 mg/mL MMT/SW/Fe_3O_4-PCA did not result any hemolysis in human blood, which suggests them to be ideal for intravenous injection. This study highlights the potential of MMT/SW/Fe_3O_4-NCs as drug delivery agent.

1. Introduction

Cancer has been humans' greatest concern as cancer is among the dominant causes of death worldwide and the rate of people diagnosed cancer is increasing nowadays. According to the International Agency for Research on Cancer, the statistic reported by GLOBOCAN expected 18.1 million of new cancer cases and 9.6 million cases of cancer deaths in 2018 globally (Bray et al., 2018), which showed an increment as compared to year 2012 (about 14.1 million new cancer cases diagnosed and 8.2 million deaths) (Torre et al., 2015). Humans are aware of cancer and they practice healthy lifestyle to reduce the risk of getting cancer, but no one can predict it as cancer is difficult to be detected and usually found at the late stage. Hence, new effective cancer screening and diagnosis approaches as well as cure for cancer are highly demanded to solve this critical disease, so as the number of human deaths due to cancer can be reduced.

In recent years, scientists have made a major breakthrough in medical field, which is the application of nanotechnology in medicine. The implementation of inorganic materials in drug delivery study becomes popular, particularly magnetite (Fe_3O_4) nanoparticles, such as in treating prostate cancer (Singh et al., 2019), lung, breast and colon cancer (Rosman et al., 2018) and cervical cancer (Malekzadeh et al., 2017). Fe_3O_4 is the only magnetic nanoparticles that is recognized by US Food and Drug Administration (FDA) for clinical use (Wang et al., 2010). For instance, Fe_3O_4 has been used in magnetic resonance imaging (MRI) contrast agent (Patsula et al., 2016) and magnetic

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